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Portal Vein Thrombosis in Association With Factor V Leiden Mutation in a Patient With Hepatocellular Carcinoma

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We report a case of hepatocellular carcinoma associated with portal vein thrombosis. Analysis of whole cellular DNA demonstrated heterozygosity for the factor V Leiden mutation. The patient also had marked protein C deficiency. The presence of the mutation associated with protein C deficiency may increase the risk of thrombosis in this patient with hepatocellular carcinoma. Med. Pediatr. Oncol. 29: 224–225, 1997. © 1997 Wiley-Liss, Inc.

Key words: hepatocelullar carcinoma; factor V Leiden; portal vein thrombosis

INTRODUCTION

Recently, a new cause of venous thrombosis called resistance to activated protein C was described [1]. More than 95% of cases of activated protein C resistance are caused by a point mutation in the factor V (FV) gene (arginine 506 to glutamine) referred to as FV Leiden [1].

Portal vein thrombosis is a relatively rare condition affecting both children and adults. In most cases, the cause of portal vein thrombosis is unknown. We describe a child with portal vein thrombosis who had hepatocellular carcinoma and was heterozygous for the FV Leiden mutation.

CASE REPORT

An 8-year-old boy was admitted to Ihsan Dogramaci Children Hospital because of abdominal distention and loss of weight. On physical examination, both the liver and spleen were palpable 10 cm below the costal margin. The hemoglobin level was 12.8 g/dl and the white blood cell count was 6,300/mm^3 with normal peripheral blood smear. The urinalysis was normal. Other laboratory workup revealed the following results: protein C (PC) 10.7% (normal 60–175%), protein S (PS) 57.7% (normal 73–210%), antithrombin III (AT III) 108% (normal 70–120%), SGOT 251 U (normal 0–50), SGPT 130 U (normal 0–40). Alpha fetoprotein was 308 IU/ml. The serum electrolytes, blood urea nitrogen (BUN), blood glucose, antiphospholipid antibodies, prothrombin time, and partial thromboplastin time were within normal range. Hepatitis B surface antigen and antibody for HBe were positive in the patient and his mother. The mother and father could not be evaluated for PC, PS, and antiphospholipid antibodies. Abdominal ultrasonography demonstrated thrombus in the intrahepatic branch of portal vein. The liver parenchyma showed increased echogenicity and calcification. There was metastatic nodular infiltration in the lungs. Abdominal computed tomography showed the presence of portal vein thrombosis and multicentric parenchymal infiltration of liver. Liver needle biopsy revealed the presence of hepatocellular carcinoma. Orsein stain was negative. The patient was treated with combination chemotherapy. Low molecular weight heparin (1 mg/kg) was administered. However, the patient died in a short period of time.

MATERIALS, METHODS, AND RESULTS

PS, PC, and AT III levels were determined by the functional test. Whole cellular DNA was isolated from peripheral blood and DNA analyzed for FV mutation. A 267-bp fragment was amplified from genomic DNA and digested with Mnl I as described previously [2]. The fragments measuring 37, 67, and 163 bp indicate the 1691 G allele, and those of 67 and 200 bp the 1691 A allele. Heterozygosity for FV mutation was detected in the patient.

DISCUSSION

Heterozygosity for FV Leiden mutation is associated with a lifelong increased risk of thrombosis but unless it is associated with other genetic defects, such as PC, PS, AT III deficiency, or acquired risk factors including in-

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fection, trauma, surgery, or intake of oral contraceptives, thrombosis may not present [3–6].

Venous or arterial thrombosis is also common in cancer patients. The pathogenesis of thrombosis in malignancies is related to a distruption in the normal balance between procoagulant and naturally occurring anticoagulant factors [7]. Treatment for cancer including chemotherapy, surgery, and radiation therapy also had impact on the hemostatic system and may alter the balance in favor of coagulation [7]. Combinations of FV Leiden mutation and PC and PS defects in our patient may play a role in development of thrombosis.

Previously it has been reported that the FV mutation was the additional risk factor for patients with PC, PS, and AT III deficiency. Decreased levels of PC and PS in this child might be either genetically inherited or secondary to liver involvement because the parents could not be evaluated for these factors. On the other hand, hepatic dysfunction was also present in the patient, probably owing to replacement of hepatic parenchyma by tumor, and this can be a major cause of alterations in the hemostatic system such as PC and PS deficiencies. Similarly, decrease in hepatic clearance of activated clotting factors may contribute to the thrombotic tendency in this case.

PS level was determined by the functional test in our patient. It has been demonstrated that the presence of the FV Leiden mutation, which is responsible for activated PC resistance, can interfere with the commercially available PS functional assay giving low levels of PS activity [8]. PS deficiency in this case may be due to underlying FV Leiden mutation. Previously 20 children with portal vein thrombosis in Brazil were studied for FV mutation and no patient was identified with this mutation. It was concluded that the FV Leiden mutation was not a risk factor for patients with portal vein thrombosis. However, the frequency of the mutation in the Brazilian population is 1.5%, a value lower than that of our country [9]. The prevalence of the mutation in our previous study was 7.1% among healthy controls, and 50% of thrombophilic patients have been reported to have a FV mutation [10,11]. Although the prevalence in the normal population of some prothrombotic mutations such as FV Leiden mutation is high, most affected individuals do not have clinically thrombotic complications, and it is probable that clinically apparent hypercoagulable states result from multigene interactions and that the development of thrombosis is precipitated by acquired prothrombotic stimuli such as the presence of hepatocellular carcinoma and combination chemotherapy in patients with an inherited predisposition to thrombosis.

A 12-year-old boy who had hepatocellular carcinoma with tumor thrombosis in the inferior vena cava was described previously by Close and Uri [12]. Nontumorous thromboembolic events were present in other organs such as the kidney, spleen, and pulmonary vessels. The PC and AT III levels were in the borderline low range. The presence of hepatocellular carcinoma associated with PC and AT III deficiencies may have potentiated each other as risk factors for developing thrombosis in their patient.

In conclusion, we believe that the presence of hepatocellular carcinoma and low level of PC may have contributed to the thrombotic risk in this case with FV Leiden mutation. The thrombogenicity of FV Leiden mutation seems to be aggravated by the additional thrombogenic risk factors in cancer patients. In order to prevent recurrent thrombosis in cancer patients with FV mutation, LMWH may be useful during the combination chemotherapy. Therefore, this mutation should be studied in all cancer patients with thrombosis.

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